

## TOTAL SYNTHESIS OF AN ANTIOXIDANT ISOLATED FROM YEAST VIA PALLADIUM-CATALYZED COUPLING AND ITS APPLICATION FOR RELATED COMPOUNDS

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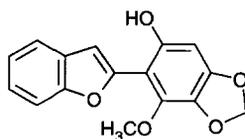
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**Abstract:** A total synthesis of an antioxidant (**1**) having a benzofuran skeleton was achieved in four steps *via* the palladium(0)-catalyzed cross-coupling reaction. We also prepared several related compounds bearing a variety of aromatic or heterocyclic rings. Some of these compounds demonstrate more potent than **1** for antioxidative activity using guinea pig liver microsomes. © 1999 Elsevier Science Ltd. All rights reserved.

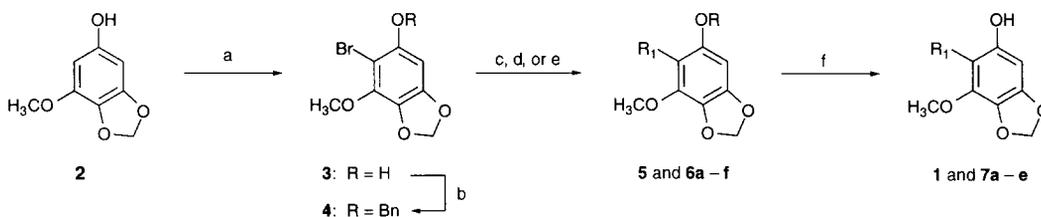
Benzofuran derivative (**1**) was isolated from various yeasts as an antioxidant<sup>1</sup> and its structure was determined by degradation studies<sup>2,3</sup>. Compound **1** was also highly active in tests including the inhibition of hemolysis of red cells. Wagner *et al.* reported the first total synthesis of **1** using the Hoesch reaction<sup>4</sup>. McKittrick and Stevenson prepared **1** with developing elegant benzofuran ring construction by way of the intramolecular Wittig reaction<sup>5</sup>. However, these methods were low yielding and limited applicability only to the synthesis of arylbenzofurans. In order to develop a facile, versatile and efficient methodology for assembling **1** and related compounds, we focused our attention on palladium(0)-catalyzed cross-coupling reaction between organometallic reagents (organoboranes<sup>6</sup> and organostannanes<sup>7</sup>) and organic electrophiles. This reaction is a powerful tool for carbon-carbon bond formation.

Herein we disclose a total synthesis of **1** *via* the palladium-catalyzed coupling reaction. We also synthesized related benzodioxole derivatives having various aromatic or heterocyclic rings and evaluated their antioxidative activity.



**1**

**Synthesis:** Scheme 1 illustrates our synthetic route. Regioselective bromination of the known benzodioxole derivative (**2**)<sup>5</sup> furnished bromobenzodioxole (**3**), a key intermediate for the synthesis of benzodioxole derivatives. Attempt on direct coupling between **3** and benzo[*b*]furan-2-boronic acid in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and P(*o*-tol)<sub>3</sub> (method A) gave only trace amounts of **1**. This problem was overcome by protection of **3** with benzyl group to give **4**. With **4** and benzofuranboronic acid in hand, palladium-catalyzed coupling gave protected arylbenzofuran (**5**)<sup>8</sup> in an excellent yield, which upon deprotection under the normal conditions afforded **1** in a 62% overall yield from **2**. Physicochemical data of the synthetic product are in good agreement with those reported values<sup>1,5</sup>.



reagents: a) Br<sub>2</sub>, AcOH, CH<sub>2</sub>Cl<sub>2</sub>; b) BnBr, NaH, DMF; c) Benzo[*b*]furan-2-boronic acid, *i*-Pr<sub>2</sub>NEt, Pd<sub>2</sub>(dba)<sub>3</sub>, P(*o*-tol)<sub>3</sub>, DMF (method A); d) ArB(OH)<sub>2</sub>, *n*-Bu<sub>4</sub>NBr, K<sub>2</sub>CO<sub>3</sub>, Pd(OAc)<sub>2</sub>, H<sub>2</sub>O (method B); e) HetSn(*n*-Bu)<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, HMPA (method C); f) H<sub>2</sub>, Pd-C, EtOAc

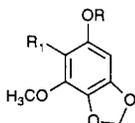
Scheme 1

This efficient methodology was applied to the synthesis of novel benzodioxole analogs. In the synthesis of the various aromatic derivatives (**7a-d**), method A was low yielding and considerable amounts of starting materials remained. Modification of the reaction conditions (base, ligand, solvent, temperature) afforded high yields of the coupling products (**6a-d**). Coupling reaction in aqueous media in the presence of *n*-Bu<sub>4</sub>NBr, K<sub>2</sub>CO<sub>3</sub>, and Pd(OAc)<sub>2</sub> (method B)<sup>9</sup> gave the desired products (**6a-d**) in excellent yields (81–100%). Subsequent hydrogenation of the resulting coupled products on Pd-C catalyst yielded the aromatic derivatives (**7a-d**)<sup>10</sup>. On the other hand, in the case of the heterocyclic derivatives Suzuki reaction failed to provide any coupled product. To our delight, tributylstannyl heterocyclic analogues reacted smoothly with **4** using Pd(PPh<sub>3</sub>)<sub>4</sub> (method C) to give the desired products (**6e**, **f**<sup>11</sup>) almost quantitatively. Cleavage of the benzyl ether in thienyl derivative (**6e**) by the catalytic hydrogenation gave a small amount of the target product (**7e**)<sup>12</sup>. Attempted deprotection under acidic conditions was led to complete recovery of **6e**. Under these deprotective conditions, furanyl derivative (**6f**) was predominantly decomposed or polymerized to give no desired compound.

**Results and Discussion:** Antioxidative activity of benzodioxole derivatives was evaluated by using the lipid peroxidation of guinea pig liver microsomes enzymatically induced with CCl<sub>4</sub><sup>13</sup>. In CCl<sub>4</sub>-stimulated lipid peroxidation, the reactive trichloromethyl free radical (CCl<sub>3</sub>•) was produced by a metabolic activation involving

the NADPH-cytochrome P-450 system<sup>14</sup>. Table summarizes the 50% inhibitory concentration (IC<sub>50</sub>) for each compound against the lipid peroxidation.  $\alpha$ -Tocopherol and *n*-propyl gallate were also tested as reference compounds and their IC<sub>50</sub> values were 280  $\mu$ M and 50  $\mu$ M, respectively.

**Table:** Antioxidative Activity for Benzodioxole Derivatives.



No.	R <sub>1</sub>	R	Method	Yield <sup>a</sup> (%)	IC <sub>50</sub> <sup>b</sup> ( $\mu$ M)
<b>1</b>		H	A	100	98
<b>7a</b>		H	B	81	83
<b>7b</b>		H	B	84	56
<b>7c</b>		H	B	100	65
<b>7d</b>		H	B	100	107
<b>7e</b>		H	C	93	44
<b>6f</b>		Bn	C	96	n.t. <sup>c</sup>

a) Isolated yields of the palladium-catalyzed reactions.

b) IC<sub>50</sub> values of reference compounds:  $\alpha$ -tocopherol = 280  $\mu$ M, *n*-propyl gallate = 50  $\mu$ M.

c) n.t. = not tested.

Modification of the ring at 5-position influenced antioxidative activity and all compounds tested were more active than tocopherol. Interestingly, among these synthesized benzodioxole derivatives, most of them exhibited higher activity than the natural product (**1**). We examined the effect of the aromatic rings at 5-position. Comparison of *para*-substituents of the phenyl moiety revealed that the relative activity profile was methoxy (**7b**) > methyl (**7c**) >> hydride (**7a**) >> phenyl (**7d**). Conversion of benzofuran to thiophene resulted in significant increase of activity (**1** vs. **7e**). These highly active compounds (**7b** and **7e**) showed equal potency to *n*-propyl gallate.

In conclusion, we have developed a facile and versatile synthesis of a natural antioxidant (**1**) by using palladium-catalyzed reaction; this reaction is demonstrated to be applicable to synthesis of novel related compounds. We also have evaluated their antioxidative activity. In this study, it was found that thienyl derivative (**7e**) and methoxyphenyl derivative (**7b**) exhibited about 2 times more potent activity than **1** and also similar activity to *n*-propyl gallate. Further structure-activity relationships studies on benzodioxole analogs are in progress.

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- 8 **5**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.95 (s, 3H), 5.01 (s, 2H), 5.95(s, 2H), 6.39 (s, 1H), 6.83 (s, 1H), 6.8–7.6 (m, 9H).
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- 10 **7a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.83 (s, 3H), 4.78 (brs, 1H), 5.91 (s, 2H), 6.31 (s, 1H), 7.32–7.34 (m, 2H), 7.37–7.41 (m, 1H), 7.46–7.50 (m, 2H).  
**7b**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.83 (s, 3H), 3.85 (s, 3H), 4.79 (brs, 1H), 5.90 (s, 2H), 6.30 (s, 1H), 7.00–7.02 (m, 2H), 7.23–7.25 (m, 2H).  
**7c**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 2.40 (s, 3H), 3.83 (s, 3H), 4.80 (brs, 1H), 5.90 (s, 2H), 6.30 (s, 1H), 7.20–7.22 (m, 2H), 7.28–7.30 (m, 2H).  
**7d**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.87 (s, 3H), 4.86 (brs, 1H), 5.91 (s, 2H), 6.33 (s, 1H), 7.35–7.41 (m, 3H), 7.44–7.48 (m, 2H), 7.63–7.65 (m, 2H), 7.68–7.71 (m, 2H).
- 11 **6f**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.91 (s, 3H), 4.96 (s, 2H), 5.92 (s, 2H), 6.36 (s, 1H), 6.47–6.48 (m, 1H), 7.27–7.33 (m, 6H), 7.52 (m, 1H).
- 12 **7e**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.91 (s, 3H), 5.21 (brs, 1H), 5.91 (s, 2H), 6.31 (s, 1H), 7.06 (dd, *J* = 0.8, 3.5 Hz, 1H), 7.15 (dd, *J* = 3.5, 5.0 Hz, 1H), 7.48 (dd, *J* = 0.8, 5.0 Hz, 1H).
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